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(54) Title: INJECTABLE BIOACTIVE GLASS COMPOSITIONS AND METHODS FOR TISSUE RECONSTRUCTION

(57) Abstract

An injectable hyaluronic acid particulate bioactive glass composition useful for the repair, reconstruction, replacement, augmentation or reconfiguration of hard bone or soft tissue anatomic structure, the composition of the glass falling within Region E of the compositional boundary diagram of Fig. 4.

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INJECTABLE BIOACTIVE GLASS COMPOSITIONS AND METHODS FOR TISSUE RECONSTRUCTION

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel injectable bioactive glass compositions for the repair of hard bone or soft tissue of human and non-human animals.

Description of the Prior Art

It has been common practice in plastic, otolaryngological and other surgeries for many years to inject or place within tissues a variety of artificial substances to repair or reconfigure anatomic structures. For example, Teflon particles have been introduced into the vocal cord and more recently into periureteral and periurethral tissues with mixed results. Disadvantages associated with this procedure include long-term progressive foreign-body reactions and migration and distant embolism associated with very small particles. Considerable research has been conducted to discover substitutes for Teflon and other conventionally employed artificial materials.

Urinary incontinence is a common accompaniment to diseases such as spina bifida and exstrophy of the bladder. The reasons for the incontinence are multifactorial and include hyperactive bladder pressure, small-capacity bladder and decreased urethral resistance. In patients who cannot void voluntarily (who do not have volitional control), the preferred method of management is to place the patient in urinary retention and empty the bladder with clean inter-mittent catheterization. This has become the hallmark of urologic management in a large percentage of patients with spina bifida. Successful management of such patients requires an adequate bladder capacity, low intravesical pressure and a normal-to-high urethral resistance. Patients with spina bifida and exstrophy of the bladder often have anatomic and physiologic findings

that are not conducive to urinary retention and clean intermittent catheterization. These findings include small bladder, high intravesical pressure and low urethral resistance. Low bladder capacity and increased intravesical pressure can, occasionally, be managed with anticholinergic medication, but this is of limited usage and most patients require enlargement of their bladders and creation of a low pressure system by augmentation cystoplasty (applying a cap of bowel to the bladder). Urethral resistance can be minimally increased with pharmacologic therapy, but his is generally unsatisfactory. Artificial urinary sphincters have been developed which can be inserted surgically. These require an open surgical operation and mechanical failure is common.

Urethral resistance can be increased by bladder neckplasty or a urethral sling procedure, both of which are open operations. Urethral resistance can also be increased by the periurethral injection of Teflon or collagen. Teflon has been used for fifteen years and does not have the permanent effect of increasing the urethral resistance. It has the unacceptable side effects in experimental animals of causing granulomas. Although clinically Teflon has been well tolerated, there have been reports of pulmonary granulomas in humans. The search for other injectable substances has resulted in the use of glutaraldehyde cross-linked bovine collagen which has been shown to increase urethral resistance. Unfortunately, experience has shown that collagen tends to break down over a period of months or years, resulting in a recurrence of incontinence.

Currently, there is a search for an injectable substance with anatomic integrity which is well tolerated by the patient. Substances such an Ivalon sponge, cut into small pieces and suspended in saline, have been suggested as suitable substitutes.

Bio-active glasses have been utilized as bone replacement materials in a variety of reconstructive surgical techniques.

These glasses have been shown to develop a strong bond with hard tissue due to a series of ion-exchange reactions between the implant surface and body fluids that result in the formation of a biologically active calcium phosphate film at the implant tissue interface [Hench et al., J. Biomed. Mater. Res., Vol. 5, pp. 117-141 (1971), and Hench et al., J. Biomed. Mater. Res., Vol. 7, pp. 25-42 (1973)]. Bio-active glasses have also been shown to form firm bonds with soft tissue [Wilson et al., J. Biomed. Mater. Res., Vol. 15, pp. 805-817 (1981); Wilson and Merwin, J. Biomed. Mater. Res.: Applied Biomaterials, Vol. 22, No. A2, pp. 159-177 (1988); and Wilson, Low et al., Biomaterials and Clinical Applications, ed. by Pizzoferrato et al, Elservier Science Publishers B.V., Amsterdam (1987)].

Certain bio-active and bio-compatible glasses and glass-ceramics (i.e., those described in U.S. Patent Nos. 4,159,358; 4,234,972; 4,103,002; 4,189,325; 4,171,544; 4,775,646 and 4,851,046) have been shown to develop a unique, strongly adherent, chemical bond with hard-bone tissue due to the influence on hydroxyapatite of the biologically active calcium phosphate film generated *in situ* by ion-exchange reactions between the glass or glass-ceramic surface and body fluids. This influence results in a strong fixation of the glass or glass-ceramic to the bone surface. Although as noted above, a variety of such glasses have been shown to bind to various soft tissue, it has been found that only a few of these glasses result in the formation of an exceptionally thin (i.e., no more than about 1-3 fibers thick), but adherent, collagen film which strongly adheres the glass to soft tissue without concomitant adverse side effects.

Failure to observe soft tissue bonding of some glasses was a consequence of inappropriate preparation of material and selection of inappropriate tissue sites, e.g., muscle. When the glass implant is successfully immobilized in appropriate soft tissue during the experimental period and when proper

histological specimens are made, soft tissue adhesion to some glasses can be confirmed and evaluated.

These particular glass compositions have also been found to advantageously become encapsulated with a thin (i.e., no more than about 1-3 fibers thick) layer of collagen after implantation.

It is an object of the present invention to provide a novel injectable composition and method for the repair, augmentation, reconfiguration or replacement of hard bone or soft tissue anatomic structures which are not subject to the disadvantages associated with presently employed materials.

SUMMARY OF THE INVENTION

The above and other objects are realized by the present invention, which provides a pharmaceutically acceptable fluid composition capable of injection via a surgical needle into a human or non-human animal and particularly adapted for the repair, replacement, reconfiguration, reconstruction or augmentation of selected hard bone and/or soft tissue anatomic structures therein comprising a homogeneous suspension in an aqueous solution of hyaluronic acid, salt or pharmaceutically acceptable derivative thereof (HA) having an average molecular weight of at least about 1 x 10^6 of at least one particulate bacteriostatic, bio-active and bio-compatible glass composition, the glass composition being one which:

(a) forms a strong adherent bond comprising a thin layer of collagen at a glass/soft tissue interface upon injection in the animal;

(b) forms a strong adherent bond comprising a layer of collagen no more than about 1-3 fibers thick;

(c) becomes encapsulated after injection in the animal with a collagen layer attached by chemical and mechanical bonding to the bio-active surface;

(d) does not result after injection in the animal in the

formation of excess scar tissue, giant cells or acute inflammatory cells; and

(e) falls within Region E of the compositional boundary diagram of Fig. 4,

wherein the particulate glass has a particle size preferably from 355μm to 100μm; the aqueous solution has a concentration of HA and the ratio of particulate glass to the aqueous solution in the suspension is such that the fluid composition remains homogeneous under pressures encountered during the injection and, following injection, the HA is bioresorbed by the animal and the particulate glass remains at the selected anatomic structures and bonds uniformly throughout the particulate surfaces thereof with the hard bond and/or soft tissue at the anatomic structures to provide anatomic integrity thereto without migration thereof or extrusion through adjacent tissue.

The invention further provides a method for the repair, replacement, reconstruction, reconfiguration or augmentation of a selected hard bone and/or soft tissue anatomic structure of a human or non-human animal comprising injecting into the anatomic structure the above-described composition.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 graphically depicts the spreading rates of varying HA compositions according to the invention.

Fig. 2 depicts a syringe and surgical needle system for delivery of the composition of the invention.

Fig. 3 graphically depicts injection force as a function of syringe volume for a single HA composition, the ratios of bio-active glass particulate/vehicle being between 0.32 and 0.4.

Fig. 4 is a ternary compositional boundary diagram of SiO_2-CaO-Na_2O glasses. Region A bounds those compositions which are bone-bonding glass formers. Ceravital(R) which is known to bond to bone tissue, but not to soft tissue, is

located within Region A. Region B comprises those compositions which are neither bone- nor soft-tissue bonding glass formers. Region C defines those compositions which form glasses that dissolve _in vivo_ when implanted in the body. Region D defines bone-bonding non-glass formers. Region E defines the compositions within Region A which form glasses capable of bonding to bone and forming acceptable thin cellular collagen bonds with soft tissue.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The following terms have the meanings and definitions normally associated therewith by those skilled in the art, except as modified hereinbelow.

The term "fluid" as used herein is intended to include any flowable and injectable liquid composition, including highly viscous compositions sometimes referred to as "pastes."

"Hyaluronic acid, salt or other derivative thereof" (HA) is intended to include hyaluronic acid, as well as salts or other derivatives naturally present in the human or non-human animal (e.g., in the vitreous humor, synovial fluid, etc.). Herein, the acronym "HA" is employed to refer to hyaluronic acid, as well as suitable salts and/or derivatives thereof.

"Pharmaceutically acceptable" is intended to include any material which is compatible with the other ingredients of the composition, which are not deleterious to the recipient thereof, have the intended function and are capable of administration to its recipient in the intended manner.

The term, when used in connection with HA, is intended to include only those HA fractions which are sterile, non-pyrogenic, non-antigenic and non-inflammatory as those terms are normally and conventionally employed in the art.

The compositions and formulations of the invention may be presented in "unit dosage form" which is intended to include all amounts, ratios, concentrations, etc., of the composition effective to achieve the desired result or condition. It will

be appreciated by those skilled in the art that dosages and dosage rates are adjusted according to the species of animal treated, magnitude of desired response and other factors routinely taken into consideration in establishing dose rates. They may be formulated by any of the methods described above or by any of the methods well known in the art of pharmacy for forming suspensions of solids in liquids.

The term "surgical needle" includes any needle adapted for delivery of the fluid compositions of the invention after injection into a selected anatomical structure. Typical such needles are used in conjunction with syringes utilizing a plunger to pressurize and deliver the composition to the intended site.

The term "anatomic structure" refers to any site or locus within the human or non-human animal, composed of hard bone and/or soft tissue, which requires repair, reconstruction, augmentation, replacement or reconfiguration to restore to transform it to a desired new configuration or state.

Exemplary of such anatomic structures treatable according to the method of the invention include vocal cords, periurethral tissue, periureteral tissue, maxilla, mandible, temporomandibular joint, chin, zygomatic arch, nose, ear, tooth root canal, tooth pulp caps, dental restoration, defects in bone, vertebral spaces, articulating joints, and subcutaneous and intradermal soft tissues.

The term "anatomic integrity" refers to the desired size, shape or configuration of a particular anatomic structure after bonding therewith of the particulate glass phase of the composition of the invention.

The term "homogeneous" as used herein is intended to include all compositions (1) not subject to preferential extrusion of one or more of the components when injected into the patient or animal and (2) not subject to segregation of one or more of the components of the mixture when allowed to stand for long periods of time.

Generally, it has been found that bio-active and bio-compatible glasses having the following weight percent compositions give satisfactory results when utilized as the particulate glass component of the invention.

Component	Weight Percentage
SiO_2	40 - 54
CaO	20 - 50
Na_2O	10 - 35
P_2O_5	2 - 8
CaF_2	0 - 25
B_2O_3	0 - 10

The following compositions have been found to yield optimum results and are, therefore, preferred.

Component	Weight Percentage
SiO_2	45.0
CaO	24.5
Na_2O	24.5
P_2O_5	6.0

Component	Weight Percentage
SiO_2	43.0
CaO	14.0
CaF_2	13.0
Na_2O	24.0
P_2O_5	6.0

Component	Weight Percentage
SiO_2	40.0
CaO	24.5
Na_2O	24.5
P_2O_5	6.0
B_2O_3	5.0

Component	Weight Percentage
SiO_2	52.0
CaO	21.0
Na_2O	21.0
P_2O_5	6.0

It will be understood that although the invention is described herein as embodying glasses falling within Region E of the ternary diagram of Fig. 4, the glasses may also contain the additional components specified above in the indicated amounts. it will be understood that such glasses still may be described as falling within Region E of Fig. 4.

The thin (1-3 fibers) collagen bond and capsule formed after implantation of the glass composition according to the invention do not thicken with time. The devices of the prior art usually fail because the included material and associated tissue response disappears with time as the material (for example, Teflon particles, hydroxyapatite particles, glass beads) is not bonded to and thus retained by the host tissues. Migration from the site removes the desired effect of tissue augmentation and provides additional hazard due to migration to other tissues with the potential for catastrophic embolism.

The particulate glass is preferably prepared according to the following method: the raw materials are mixed in a Nalgene container on a ball mill for four hours. The mix is then melted in a platinum crucible at 1350°C and homogenized for 24 hours. The molten glass is poured into distilled-deionized water to produce a glass frit. the frit is ground in a mortar and pestle and passed through ASTM sieves to produce the required particle size range.

The primary variables affecting the rheology of the bio-active compositions of the invention and the ability to inject through typical 16-18 gauge needles are: maximum particle

size, range of particle sizes, ratio of the weight of glass particles to the weight of hyaluronic acid solution, and percentage of hyaluronic acid in solution.

Each of these parameters may, of course, be varied to optimize the composition for a particular application.

Particles larger than 45 mesh ASTM Standard (355μm) cannot be injected through a 16 gauge needle without unduly decreasing the volume of glass powder in the paste by a significant amount. Since the objective is to deliver as large a quantity of particles per injection as possible, the practical upper limit in particle size is about 355μm.

Particles smaller than 100μm are subject to macrophage attack <u>in vivo</u>. Since the objective is to retain the maximum number of particles in the tissues per injection, this establishes the lower limit of particle size at about 100μm.

Selection of polymer for the injectable composition requires meeting three criteria: (1) the polymer must be bioresorbable with no negative biological responses, i.e., it must be metabolized relatively quickly and with no deleterious effects; (2) the rheological properties must be such that a relatively small quantity when mixed with a large volume of glass particulate will create a solution with a paste-like consistency which can be extruded through a needle; and (3) the viscosity/shear properties of the polymer must not lead to preferential extrusion or segregation of the polymer during injection.

Hyaluronic acid, as well as its pharmaceutically acceptable salts and derivatives, meet each of the three criteria above. As reviewed by Balazs et al. [Proc. 5th Annual Conf. Biotechn. CMC Corp., pp. 1-8, 1988], the rate of removal of HA from the anterior chamber of the eye is only 1-2 days half-life and removal from blood is only 2-5 minutes half-life. The removal is via the liver endothelium where it is completely broken down chemically and eliminated [Frazer et al., <u>Clin. Exp. Pharm. Phys.</u>, Vol. 11, pages 17-25, 1984].

Balazs and Denlinger [CIBA Foundation Symp. #143, pp. 265-280, 1989] state that the unique rheological properties of the hyaluronan molecule stem from its large molecular volume and from its extensive interactions with and entanglement of the molecular coils. In only a 0.02% solution, the HA molecules with a 2-4 million molecular weight per molecule have such a large volume that the molecules are touching and form a crowded network. For a 2% solution, the molecules are 100 times more crowded. However, since the network is not cross-linked, it is readily deformed by mechanical forces, such as a moving plunger in a syringe. Under low shear rates, e.g., slow-speed injection, the network shows high viscosity. Under rapid shear rates, the viscosity decreases. Decreasing the percentage of HA in solution decreases the viscosity and viscosity/shear dependence.

EXAMPLE 1

The glass powders are mixed with HA molecular solutions in the range of 1%, 1.2%, 1.4%, 1.8% and 2%, and the spreading rates of the resultant pastes were tested. These experiments are summarized in Fig. 1. They show that for solutions up to and including 1.8% HA, the pastes continued to spread under pressure. The conclusion from this experiment is that HA gel viscosity increases linearly with concentration in solution. Since (1) the gel's seepage (preferential extrusion) through the paste decreases with increasing viscosity, (2) gel seepage must be avoided to ensure good quality injections, and (3) a 2% HA solution is still sufficiently pliable to allow easy manipulation, but minimizes seepage, a 2% HA solution is preferably used in the paste.

EXAMPLE 2

The optimal ratio of polymer to glass particulate to

achieve a paste capable of being injected through 16-20 gauge needles was determined as follows:

A given quantity of glass particulates of 45-120 mesh were weighed and a 1% HA solution was added as required to produce ratios from 0.33 glass/HA to 1.6 glass/HA. The powder and polymer were mixed with a spatula using a stirring and spreading motion until homogeneity was achieved (approximately one minute). The paste was loaded into the top of a large syringe and then injected into a smaller syringe with has a 16 or 20 gauge needle or no needle. It was discovered that this method of loading eliminates air bubbles in the paste. The paste was injected through the needle using moderate speed and pressure, and the relative smoothness of the injected volume was noted by manual manipulation. Segregation of the polymer, which must be avoided, eliminated glass particles from the injected material which could be detected by feeling it, although microscopy was also used to verify the findings.

The results of this test series are shown in Table 1 with the ratios passing through the (a) small syringe, (b) small syringe with a 20 gauge needle, and (c) small syringe with a 16 gauge needle. With a ratio of 0.4 glass particulate/HA, the paste passed through both sizes of needle with no clogging. The optimal ratio within the given particle size range corresponds to 2.5 parts of HA to 1 part of glass particulate.

TABLE 1

Parameter Variation and Injection Results

Glass/HA Syringe Only	HA Volume (ml)	Mesh Size	Volume of Clog (ml)
1.0	0.5	25 - 45	0.25
1.0	0.5	25 - 35	0.30
1.0	0.5	35 - 45	0.22
1.0	0.1	35 - 45	--
1.0	0.1	45 - 120	--
1.0	0.5	45 - 120	--
1.4	0.5	45 - 120	0.01
1.6	0.5	45 - 120	0.14
1.5	0.5	45 - 120	0.06
1.375	0.4	45 - 120	0.04
1.25	0.4	45 - 120	--
Glass/HA Syringe Only	**HA Volume (ml)**	**Mesh Size**	**Volume of Clog (ml)**
1.0	0.1	45 - 120	--
1.0	0.5	45 - 120	0.22
1.0	0.3	80 - 120	0.13
0.5	0.3	80 - 120	0.04
0.4	0.3	80 - 120	--
0.4	0.5	80 - 120	0.02
0.4	0.4	80 - 120	--
0.33	0.5	45 - 120	0.02
Glass/HA 16 Gauge Needle	**HA Volume (ml)**	**Mesh Size**	**Volume of Clog (ml)**
0.5	0.5	45 - 120	--
0.5	0.3	35 - 120	--
0.33	0.5	35 - 120	--
0.67	0.5	45 - 120	0.13
0.40	0.5	45 - 120	--

The relative roundness of the glass particles also affects the rheology of the paste and the optimal ratio of glass to HA. For particles with sharp corners, as produced by crushing of glass, the optimal ratio is 0.4, as determined above. With completely round particles, the ratio can be increased slightly when all other parameters are unchanged. The final optimal ratio, however, will be slightly less than 0.4.

Rounding of the crushed glass sufficient to improve the rheology can be accomplished by milling dry without a milling medium for 48 hours and sieving off the finer particles.

The configuration of the syringe used for the delivery of the injectable paste is also an important variable for optimizing the method of the invention. A design which minimizes the force needed for paste injection and thus maximizes the amount of glass in the paste and minimizes the seepage of HA during extrusion at clinical injection rates is given in Fig. 2. The critical design features are barrel and die L/D ratios, barrel/die diameter ratios and the die taper angle.

Referring to Fig. 2, a syringe/needle assembly consists of barrel 12, plunger 14 and syringe tip 16. Preferred dimensions of the assembly for injecting optimum pastes according to the invention are as follows: The thickness represented by arrows (a) of the plunger cap 18 and grip flange 20 is 0.1 cm. The diameter of the plunger cap [arrow (b)] is 1.414 cm. The diameter of the grip flange [arrow (c)] is 1.714 cm. The length of the barrel [arrow (d)] is 11.5 cm. The distance [arrow (e)] between the plunger cap 18 and grip flange when fully depressed is 0.5 cm. The distance between the plunger cap 18 and the end of the barrel [arrow (f)] when fully depressed is 12.0 cm.

The diameter [arrow (g)] of the plunger is 0.614 cm and the inner diameter [arrow (h)] of the barrel is 0.714 cm. The length of the taper of the proximal end of the barrel to the beginning of the syringe tip 16 [arrows (i)] is 0.166 cm. The

angle (α) between the tape wall at the end of barrel 12 and the longitudinal axis of the barrel 12 is 65°. The taper of the syringe tip 16 from the end of the barrel 12 is a standard Luer taper. The outer diameter of the proximal end of the syringe tip 16 is 0.155 cm. The length of the tapered syringe tip 16 [arrow (j)] is 0.170 cm.

EXAMPLE 3

The ideal syringe volume is a compromise between ease of use and sufficient paste volume delivery. Since a total of 10-12 ml of the paste needs to be injected in at least three sites in clinical practice to treat urinary incontinence, a 3-4 ml syringe is desirable. Also, experiments show that the least force is needed to inject pastes when the syringe volume is about 4 ml (Fig. 3). This is totally unexpected in view of the theoretical predictions for injectable mixtures.

EXAMPLE 4

Two bio-active glass compositions having the following composition were employed in this experiment:

45S5 Composition	43S5 4F Composition
45% SiO_2	43% SiO_2
24.5% CaO	14% CaO
24.5% Na_2O	13% CaF_2
6% P_2O_5	6% P_2O_5

The particle sizes ranged from 100-355μm and were suspended in medical grade HA acid, so as to be injectable through a #16 needle. An injection of 0.1 ml was made into the dome of the bladder in rabbits and subcutaneous injections of both suspensions and of the HA acid alone were made (six subcutaneous injections in each animal). Two rabbits were

killed after each of 2, 4, 6, 8, 10 and 12 weeks. All experimental sites were examined microscopically, as were major internal organs. Samples of liver, kidney, lungs and lymph nodes were digested and analyzed by AAS for silicon from migrating particles.

Particulate material was present in 67% of injection sites in the bladder overall. No difference in tissue response was seen between glass compositions. Soft tissue bonding to the particles' surface was seen at all time periods. There was persistent cellularity within the particulate mass at all time periods, although there was no inflammation in adjacent tissues and the urothelium was invariably normal.

Subcutaneous sites which contained HA were completely normal at all time periods. The material could not be detected by normal histological techniques. There was no difference between glass compositions at any time. Many of the injections were in the subdermal muscle planes rather than subcutaneous tissues. Tissue response showed bonding of soft tissues at all time intervals, but with persistent cellularity throughout the experimental period. Particles toward the periphery of the mass had thin collagenous tissue around them and no macrophages at the interface and those in the center had macrophages, giant cells and some focal inflammation between them. There was no inflammatory infiltrate in surrounding tissues. In some cases, the central part of the lesion was infarcted, although the peripheral particles were bonded in place.

Histological examination of liver, lungs, lymph nodes and kidneys revealed no particles nor any toxicological effect. Chemical analysis showed no increase of silicon in tissues.

In this rabbit model, the material frequently came to rest in muscle rather than fibrous connective tissue and the quantity injected was greater than is required clinically. The continuous movement of the host tissues produced significant cellularity inside the lesion due to abrasion of the ingrowing tissues. The peripheral particles were invariably bonded in

place without such cellularity and there was no effect on other tissues whether local or distant. The ability of HA to provide an injectable vehicle which is completely metabolized within the first two weeks was confirmed.

Overall, eight out of twelve bladder sites were identified and retrieved at autopsy. The particles were present in the bladder wall between muscle fibers underlying the urothelium. They were surrounded by collagen fibers and cellular connective tissue at all times up to twelve weeks. There was no inflammation around the site and the overlying urothelium was normal. This tissue response is as expected in a moving muscle bed; the particles are immobilized, but abrasion of the tissues occurs with every expansion and contraction of the bladder wall. No difference was seen between 45S5 and 43S5 4F injections. In cases where the particulate material was not found, it was assumed that it was either retained in the syringe or injected through the bladder wall into the lumen.

No change attributable to the materials was seen in liver, kidney, lung or bronchus in any animal at any time. Retrieval rate of drainage lymph nodes was very low; the few which were found were normal. It is assumed that the fact that drainage lymph nodes were not affected made them difficult to detect. Chemical analyses of these soft tissues showed no increase of silicon in tissues.

HA injected sites were completely normal at all time periods. The tissue response to the glass materials was evaluated using the following criteria:

1. Bonding of collagen fibers to the surface of particles.
2. Presence of phagocytic cells at the interface.
3. State of the tissue surrounding the mass, which is presumably more easily stabilized.
4. State of the tissue in the center of the mass, which is presumably more prone to movement and is likely to take longer to stabilize.

5. Cellular response in adjacent tissues.

The tissue response was variable. Soft tissue bonding was seen from four weeks, but phagocytes were present at all time intervals, although reducing in numbers throughout the experimental period. The outside of the mass was generally relatively acellular stable connective tissue, the inside was often more cellular and the fibers more fragile. Some masses had foci of degenerative change centrally. These effects are due to mechanical abrasion of the ingrowing collagen fibers and the new capillaries by the glass particles. There was no inflammation or infiltration of adjacent tissues. No difference was seen between 45S5 and 43S5 4F bio-active glass sites.

In this model, effects due to movement in the tissues must be separated from those due to the material. The combination of HA and glass particulates could be injected. In the tissues, the HA produced no detectable effect, being removed without trace as predicted. The glass particulates were bonded to the collagen fibers of the connective tissue and were effectively retained in tissue up to twelve weeks. The presence of persistent cellularity, phagocytosis and some necrosis is attributable to mechanical damage in tissues. The amounts of injection which are recommended for clinical use, being much smaller, will not cause this problem.

CLAIMS

1. A pharmaceutically acceptable fluid composition capable of injection via a surgical needle into a human or non-human animal and particularly adapted for the repair, replacement, reconfiguration, reconstruction or augmentation of selected hard bone and/or soft tissue anatomic structures therein comprising a homogeneous suspension in an aqueous solution of hyaluronic acid, salt or pharmaceutically acceptable derivative thereof having an average molecular weight of at least about 1 x 10^6, of at least one particulate bacteriostatic, bio-active and bio-compatible glass composition, said glass composition being one which:

   a. forms a strong adherent bond at a glass/hard bone tissue interface upon injection in said animal;
   b. forms a strong adherent bond at a glass/soft tissue interface upon infection in said animal;
   c. becomes encapsulated after injection in said animal with a thin collagen layer;
   d. does not result after injection in said animal in the formation of excess scar tissue, giant cells or acute inflammatory cells; and
   e. falls within Region E of the compositional boundary diagram of Fig. 4,

wherein said particulate glass has a particle size; said aqueous solution has a concentration of said hyaluronic acid, salt or derivative thereof and the ratio of particulate glass to said aqueous solution in said suspension is such that said fluid composition remains homogeneous under pressures encountered during said injection and, following injection, said hyaluronic acid, salt or derivative thereof is bioresorbed by said animal and said particulate glass remains at said selected anatomic structures and bonds uniformly throughout the particulate surfaces thereof with said hard bone and/or soft tissue at said anatomic structures to provide anatomic

integrity thereto without migration thereof or extrusion through adjacent tissue.

2. A composition according to claim 1, wherein said aqueous solution contains hyaluronic acid.

3. A composition according to claim 1, wherein said aqueous solution contains sodium hyaluronate.

4. A composition according to claim 1, wherein said bacteriostatic, bio-active and bio-compatible glass has the following weight percentage composition:

Component	Weight Percentage
SiO_2	40 - 54
CaO	20 - 50
Na_2O	10 - 35
P_2O_5	2 - 8
CaF_2	0 - 25
B_2O_3	0 - 10.

5. A composition according to claim 4, wherein said bacteriostatic, bio-active and bio-compatible glass has the following weight percentage composition:

Component	Weight Percentage
SiO_2	45.0
CaO	24.5
Na_2O	24.5
P_2O_5	6.0.

6. A composition according to claim 4, wherein said bacteriostatic, bio-active and bio-compatible glass has the following weight percentage composition:

Component	Weight Percentage
SiO_2	43.0
Na_2O	24.0
CaO	14.0
CaF_2	13.0
P_2O_5	6.0.

7. A composition according to claim 4, wherein said bacteriostatic, bio-active and bio-compatible glass has the following weight percentage composition:

Component	Weight Percentage
SiO_2	40.0
CaO	24.5
Na_2O	24.5
P_2O_5	6.0
B_2O_3	5.0.

8. A composition according to claim 4, wherein said bacteriostatic, bio-active and bio-compatible glass has the following weight percentage composition:

Composition	Weight Percentage
SiO_2	52.0
CaO	21.0
Na_2O	21.0
P_2O_5	6.0.

9. A method for the repair, replacement, reconstruction, reconfiguration or augmentation of a selected hard bone and/or soft tissue anatomic structure of a human or non-human animal, comprising the step of injecting into said anatomic structure a composition which itself comprises a homogeneous suspension, in an aqueous solution of hyaluronic acid, salt or pharmaceutically acceptable derivative thereof, of at least one

biocompatible glass composition, wherein:

a. said glass composition is in the form of particles;
b. the ratio of glass particles to said aqueous solution is such that the suspension remains homogeneous under pressures normally encountered during injection; and
c. following injection, said hyaluronic acid, salt or pharmaceutically acceptable derivative thereof is bioresorbed by said animal, and said glass particles remain at said anatomic structure and bond therewith to provide anatomic integrity thereto.

16. The method of claim 9 wherein the sizes of said particles are within the range 100-355 μm.

17. The method of claim 9 wherein the bioactive glass composition falls within Region E of the compositional boundary diagram of Fig. 4.

18. The method of claim 9 wherein said anatomic structure comprises periurethral tissue.

19. The method of claim 9 wherein said anatomic structure comprises periureteral tissue.

20. The method of claim 9 wherein said anatomic structure comprises maxillofacial tissue.

21. The method of claim 9 wherein said anatomic structure comprises mandibular tissue.

22. The method of claim 9 wherein said anatomic structure is tooth root canal or pulp cap.

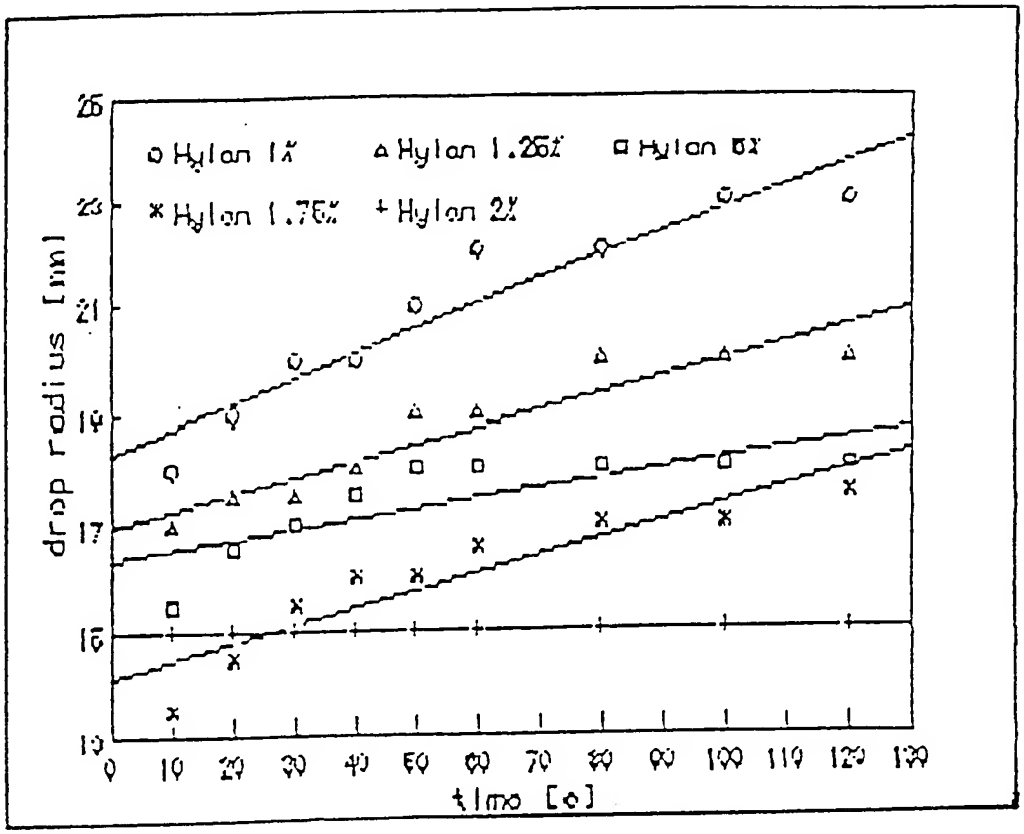
23. The method of claim 9 wherein said anatomic structure is the vocal cords.

24. The method of claim 9 wherein said anatomic structure is defective bone.

25. The method of claim 9 wherein said anatomic structure is a vertebral space.

26. The method of claim 9 wherein said anatomic structure is an articulating joint.

27. The method of claim 9 wherein said anatomic structure includes subcutaneous or intradermal soft tissue.



o Hylan 1%
Δ Hylan 1.25%
□ Hylan 5%
* Hylan 1.75%
+ Hylan 2%
drop radius [mm]
time [s]

Figure 1

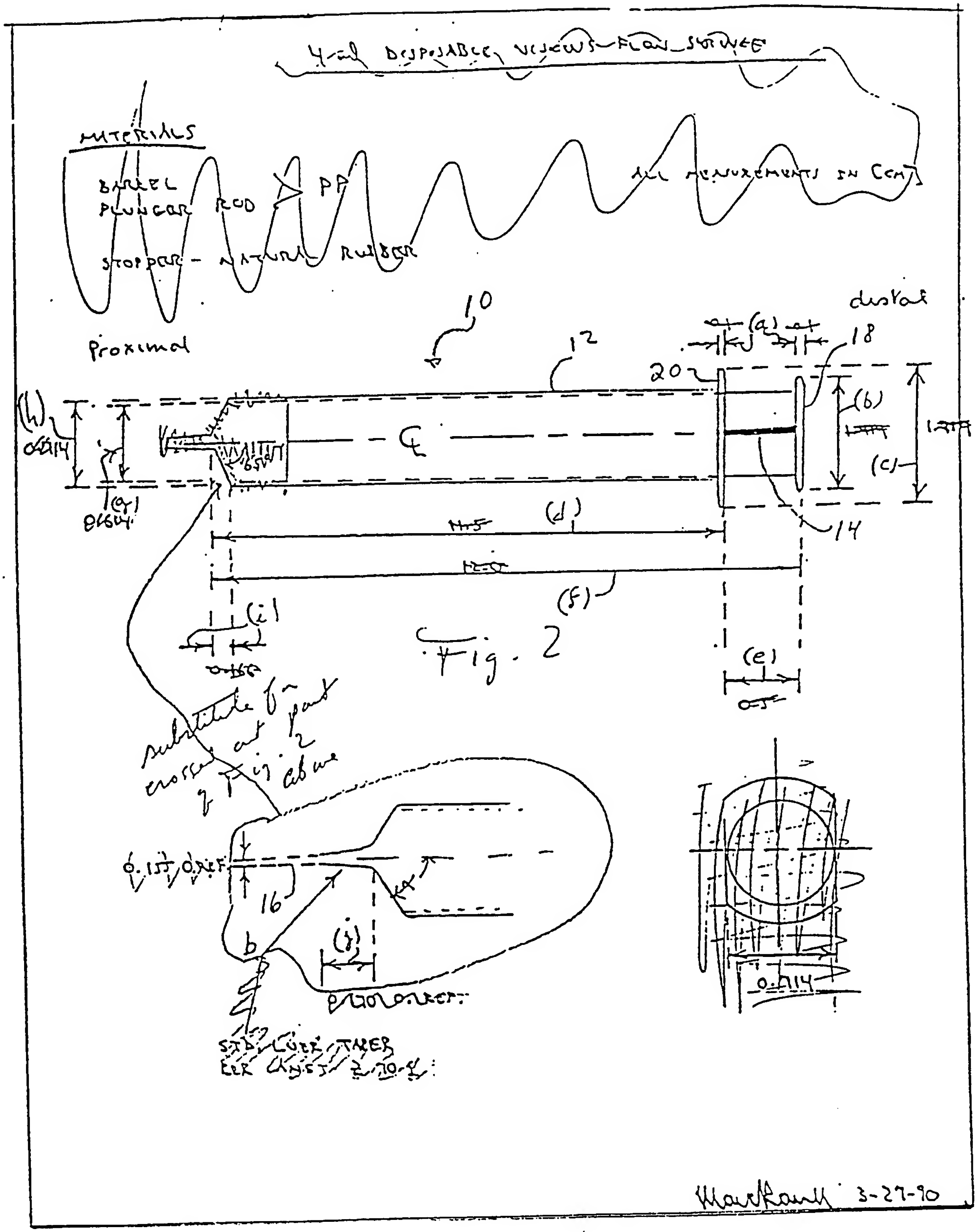


Fig. 2

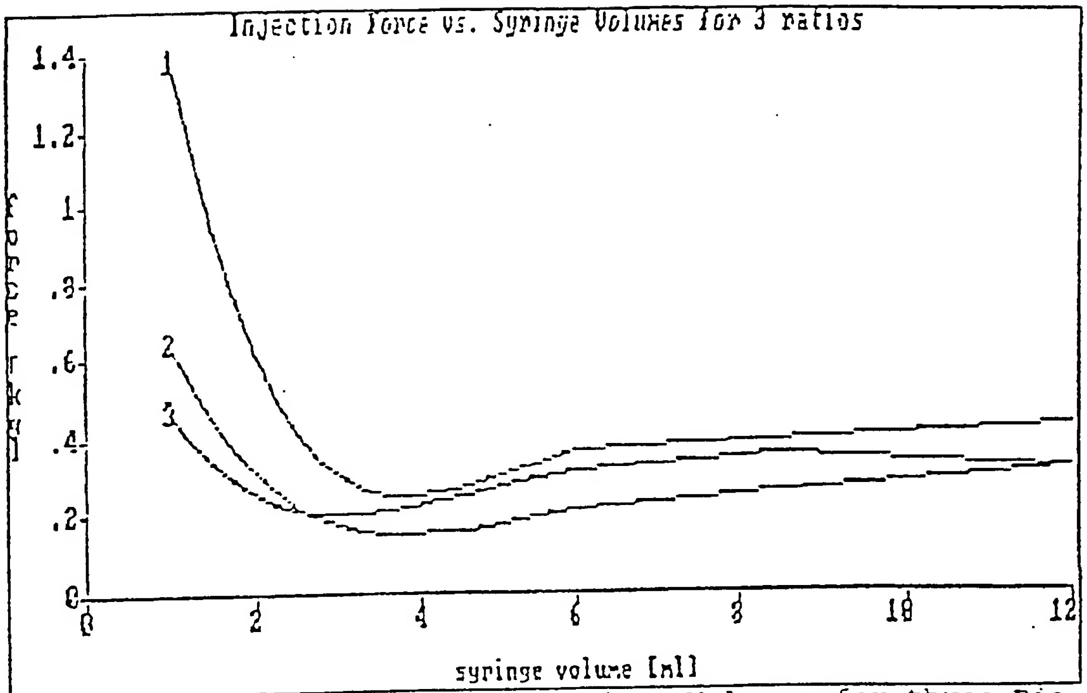


Figure 3: Injection Force vs. Syringe Volumes for three Bio-glass/Hyaluron ratios. Ratio 1 = 0.32, ratio 2 = 0.36, ratio 3 = 0.40.

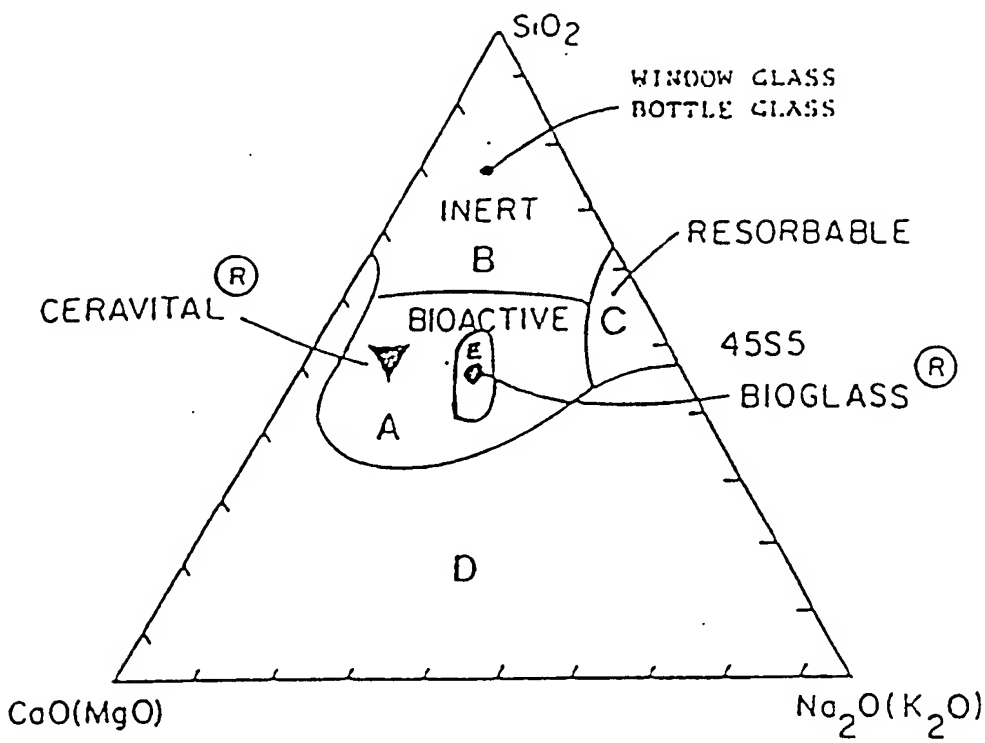


Figure 4 Compositional Diagram showing soft tissue bonding area (E) within the bone bonding area (A).